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(71) Applicant
L'Oreal

(Incorporated in France)

14 rue Royale, Paris 75008, France

(72) Inventor
Didier Saint Leger

(74) Agent and/or Address for Service
J A Kemp and Co
14 South Square, Gray's Inn, London, WC1R 5EU, United Kingdom

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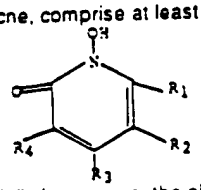
(54) Pharmaceutical and cosmetic compositions based on pyridones and antibacterial agents

(57) Topical compositions for the treatment of acne, comprise at least one pyridone derivative:



(I)

in which:

R_1 is H, C_{1-17} alkyl, C_{5-8} cycloalkyl, cycloalkylalkylene group, the alkylene group having from 1 to 4 carbon atoms, aryl, aralkyl, the alkyl group having from 1 to 4 carbon atoms, arylalkenyl, the alkenyl group having from 2 to 4 carbon atoms, the aryl and cycloalkyl groups optionally substituted with C_{1-4} alkyl or alkoxy;

R_2 is H, C_{1-4} alkyl, C_{2-4} alkenyl, halogen atom or benzyl;

R_3 is H, C_{1-4} alkyl or phenyl; and

R_4 is H, C_{1-4} alkyl, C_{2-4} alkenyl, methoxymethyl, halogen or benzyl; as well as their cosmetically or pharmaceutically acceptable salts, and at least one antibacterial agent chosen from macrolide antibiotics and pyranosides, as well as their salts or esters. Preferred compositions contain octopirox or cyclopirox and erythromycin or clindamycin.

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Pharmaceutical and cosmetic compositions based on pyridones and on antibacterial agents

The present invention relates to new compositions based on pyridone derivatives and on antibacterial agents of the macrolide and the pyranoside family, intended for use in treatments of dermatoses such as acne and in the cosmetic treatment of the skin.

The aetiopathology of acne, although poorly defined, owes its origin to the formation of a characteristic lesion, the comedo. The latter results from the obstruction of the pilosebaceous duct as a consequence of dyskeratinization of the region of the infundibulum of the duct.

This obstruction has the major effect of modifying the rheological properties of the sebum, and the physiochemical properties of the medium. This modification leads to the hyperproliferation of the cutaneous resident strains, which trigger an inflammatory type reaction of the body.

Two types of lesions are generally distinguished.

The first type corresponds to the so-called open comedo or blackhead, the clinical feature of which is commonplace and whose development remains limited. This type of comedo may be readily removed, either by extrusion, or by physical or chemical treatment by the use of topical agents known as keratolytics, which are well known per se.

The second type corresponds, initially, to the

development of the so-called closed comedones or microcysts, the final stage of which is the rupture of the pilosebaceous follicle which has produced it and which releases into the dermis numerous inflammatory products inducing reaction of the host body.

The lesions which characterize inflammatory acne are hence intermediate stages of the microcysts, and are grouped together under the generic names of papules, pustules, nodules or cysts, nodulocystic acne representing the most severe form of acne.

At the present time the products which generate the inflammation, or the mechanisms by which they generate the inflammation, remain poorly defined, although many clinical experiments suggest that the bacterial flora, of which Propionibacterium acnes is the major representative, are strongly implicated.

It is known that the topical or systemic use of antibiotic compounds, such as erythromycin, clindamycin, lincomycin or their derivatives, in the therapy of acne has as its immediate consequence a very obvious anti-inflammatory effect.

It is thought, moreover, that certain skin yeasts, in particular Pityrosporum ovale or Pityrosporum orbiculare yeast, are present in the inflammatory acne lesions, and it has been shown that Pityrosporum ovale was one of the primary causes of certain inflammatory skin conditions such as dandruff (pytiriasis capitis) and seborrheic

dermatitis.

During the rupture of the comedo, the Pityrosporum ovale yeast, or its transitory forms, are released and also generate inflammation.

The Applicant has discovered, and this forms the subject of the invention, that by combining pyridone derivatives and antibacterial agents chosen from macrolide antibiotics and pyranosides, it was unexpectedly possible to improve the treatment of acne.

The Applicant has discovered that the combination of antifungal agents, of the pyridone derivative type, and antibacterial agents mentioned above combats the inflammation due to acne much more rapidly and more effectively than an antifungal agent alone or an antibacterial agent alone.

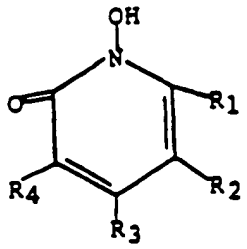
The subject of the invention is hence a pharmaceutical composition intended for the treatment of acne, combining a pyridone derivative with certain antibacterial agents.

Another subject of the invention consists of the use of the composition defined above for the preparation of a composition for treating acne.

Other subjects of the invention will become apparent on reading the description and the examples which follow.

The composition intended for a topical application for the treatment of acne is essentially characterized in that it contains, in a physiologically acceptable medium,

at least one pyridone derivative corresponding to the formula:



(I)

in which:

R_1 denotes a hydrogen atom, a linear or branched alkyl group having from 1 to 17 carbon atoms, a cycloalkyl group having from 5 to 8 carbon atoms, a cycloalkylalkylene group, the alkylene group having from 1 to 4 carbon atoms, an aryl group, an aralkyl group, the alkyl group having from 1 to 4 carbon atoms, an arylalkenyl group, the alkenyl group having from 2 to 4 carbon atoms, it being possible for the aryl and cycloalkyl groups to be substituted with an alkyl group having from 1 to 4 carbon atoms or alternatively an alkoxy group having from 1 to 4 carbon atoms;

R_2 denotes hydrogen, alkyl having from 1 to 4 carbon atoms, alkenyl having from 2 to 4 carbon atoms, a halogen atom or a benzyl radical;

R_3 denotes hydrogen, alkyl having from 1 to 4 carbon atoms or phenyl; and

R_4 denotes hydrogen, alkyl having from 1 to 4 carbon atoms, alkenyl having from 2 to 4 carbon atoms, methoxymethyl or a halogen atom or a benzyl radical, as well as their cosmetically or pharmaceutically acceptable salts, and at least one antibacterial agent chosen from

macrolide antibiotics and pyranosides, as well as their salts or esters.

Especially preferred compounds of formula (I) are those for which R_1 denotes a cyclohexyl group and R_3 a lower alkyl group, or alternatively those for which R_1 denotes a linear or branched alkyl group and R_3 a lower alkyl group. Among these compounds, those which are more especially preferred are 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridone, known as Ciclopirox, when it is in the form of an ethanolamine salt, and 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1H)-pyridone, known as Octopirox, when it is in the form of an ethanolamine salt.

Especially preferred antibacterial agents are chosen from:

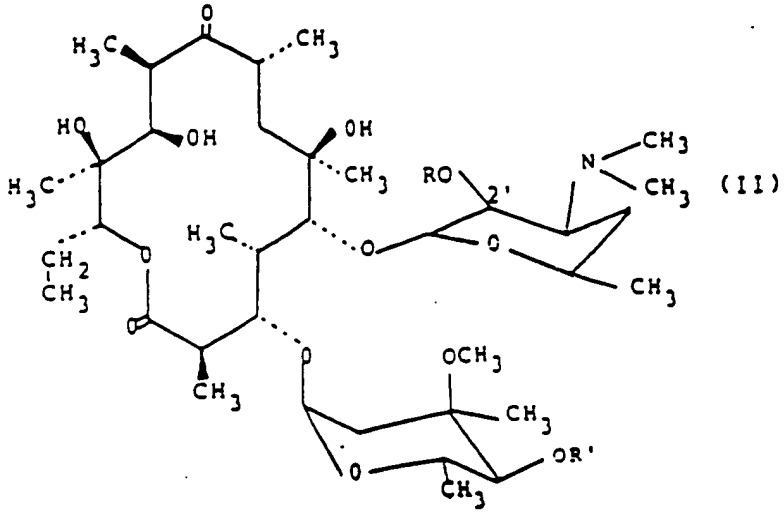
erythromycin derivatives, such as erythromycin, its salts and its esters, and more especially erythromycin estolate, erythromycin ethylcarbonate, erythromycin ethylsuccinate, erythromycin glucoheptonate, erythromycin lactobionate, erythromycin propionate lauryl sulphate, erythromycin linoleate, erythromycin propionate, erythromycin stearate, monoenic esters such as erythromycin A monooleate;

the clindamycin derivatives are the hydrochlorides, palmitates and phosphates; and

the lincomycin derivatives are the hydrochlorides.

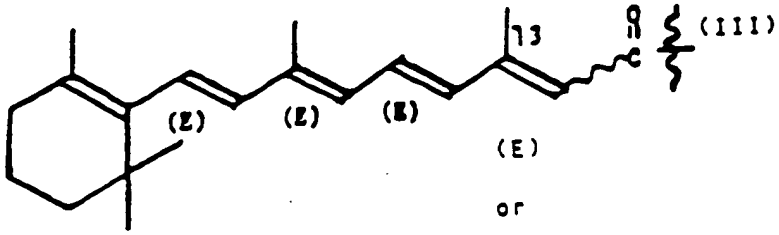
A preferred embodiment consists in using erythromycin retinoates, clindamycin retinoates or lincomycin

retinoates as antibacterial agents. Such compounds are, in particular, described in French Patent Application No. 86/06,528. The compounds in question are, more especially, the retinoic esters at the 2'-position of erythromycin A, and the retinoic esters at the 3-position of lincomycin and of clindamycin. The retinoic esters at the 2'-position of erythromycin A may be represented by the following formula:



(II)

in which R denotes an all-trans-retinoyl radical or a 13-cis-retinoyl radical and R' denotes H; the retinoyl radical having the formula:



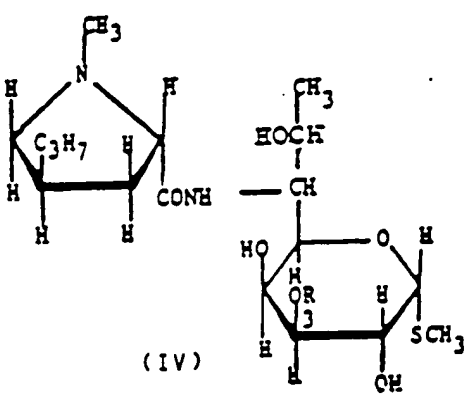
(III)

(E)

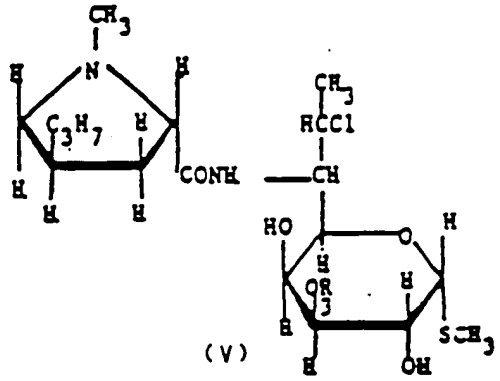
or

(Z)

The retinoic esters at the 3-position of lincomycin and of clindamycin may be represented by the following formulae:



(IV)



(V)

in which R has the same meaning as that given above.

These compounds may be prepared by various esterification processes, and especially an esterification carried out in an anhydrous organic solvent medium, preferably in tetrahydrofuran alone or mixed with another organic solvent such as pyridine, by reacting an excess of mixed anhydride of carbonic and all-trans- or 13-cis-retinoic acids (prepared in situ, for example, from ethyl chloroformate and all-trans- or 13-cis- acid) with erythromycin A, lincomycin and clindamycin in base form, in the presence of an organic or inorganic base such as pyridine and/or sodium hydrogen carbonate.

Another esterification process consists, in particular for lincomycin and clindamycin, in using the imidazolides of retinoic acids in an anhydrous solvent such as N,N-dimethylformamide, in the presence of a base

such as sodium tert-butylate or potassium tert-butylate, leading to a mixture of retinoic esters of these antibiotics.

Other erythromycin A derivatives described, in particular, in FR-A-2,582,000, are represented by the formula (II), in which :

R or R' denotes a di- or trienic C_{18} linear acyl radical of all-cis (Z) stereochemical configuration, and the remaining R' or R denotes a hydrogen atom.

According to a preferred embodiment, R or R' denotes the following radicals:

(9Z, 12Z)-octadecadienoyl or linoleoyl

(9Z, 12Z, 15Z)-octadecatrienoyl or α-linolenoyl, and

(6Z, 9Z, 12Z)-octadecatrienoyl or γ-linolenoyl.

2'-O-linoleylerythromycin A, 4"-O-linoleyleryth-romycin A and 4"-O-(α-linoleyl)erythromycin A may be mentioned in particular.

These compositions can also contain other compounds, such as known substances capable of having an effect on the treatment of acne, and in particular S-carboxymethylcysteine, thiamorpholinone, S-benzylcysteamine and their derivatives, and tioxolone.

In one embodiment, the compositions according to the invention contain keratolytic agents such as, for example, salicylic acid in proportions from 0.01 to 10%

by weight, benzoyl peroxide in proportions from 0.01 to 10% by weight, resorcinol in proportions from 0.01 to 5% by weight, retinoic acid and its derivatives, as well as humectants such as, for example, glycerin and urea.

In another embodiment, the compositions also contain steroidal or non-steroidal anti-inflammatory agents such as, more especially, hydrocortisone, indomethacin, glycyrrhetinic acid, α-bisabolol, betamethasone, fluocinolone acetonide and desoxymethasone.

The pyridone derivatives are preferably used in proportions from 0.01 to 5% by weight relative to the total weight of the composition, and the antibacterial agents in proportions from 0.01 to 5% by weight relative to the total weight of the composition.

Hydrocortisone or indomethacin, when they are present, are present in proportions also of between 0.01 and 5% by weight relative to the total weight of the of the composition.

The compositions according to the invention may be presented in various forms, such as gel, pad, cream, lotion, spray, foam, powder, ointment, stick, cake or liquid soap form.

The compositions can also contain adjuvants customarily used in pharmaceutical compositions applied on the skin, and in particular water or mixtures of water and solvents such as lower alcohols, for example ethanol or isopropanol, ethylene glycol, ethylene glycol monomethyl,

monoethyl or monobutyl ethers, propylene glycol, propylene glycol monomethyl ether and dipropylene glycol monomethyl ether, antioxidants and thickeners.

The therapeutic treatment of acne according to the invention is preferably carried out according to a process that consists in applying a sufficient quantity of the composition according to the invention two or three times per day on the areas of the skin to be treated, continuing this for a period of 6 to 30 weeks, and preferably 12 to 24 weeks.

The compositions according to the invention can be used preventively, in particular on the areas of skin likely to be affected by acne.

The compositions according to the invention may also be used for the cosmetic treatment of the skin; in particular, they enable comedones to be treated and facilitate extrusion of the latter, and hence cleanse the skin.

The Applicant found that the compositions according to the invention not only enabled a very rapid improvement to be obtained in the inflammatory state of acne, but also enabled a decrease to be brought about in the lesions of the so-called first type, the feature of which is that they are non-inflammatory.

The examples which follow are designed to illustrate the invention, no limitation of the latter being implied.

PREPARATION EXAMPLE 1

Preparation of 2'-O-(13-cis-retinoyl)erythromycin A

5 g (16.6 mmol) of 13-cis-retinoic acid are dissolved in 35 ml of anhydrous tetrahydrofuran in a round-bottomed flask and under an inert atmosphere; the reaction mixture is cooled to 0°C and then 3 ml (38 mmol) of anhydrous pyridine and 1.6 ml (16.6 mmol) of ethyl chloroformate are poured in. The solution is stirred for 5 minutes and 2.5 g (30 mmol) of sodium hydrogen carbonate are added, followed by 4.9 g (6.7 mmol) of erythromycin A, previously dissolved in 150 ml of tetrahydrofuran. The reaction mixture is then left with stirring for 10 hours while being allowed to return to room temperature (thin layer chromatography on silica gel: methylene chloride/methanol, 10%). The solution is poured into 60 ml of water and then extracted with ethyl acetate. The organic phase is dried over magnesium sulphate, filtered and then concentrated under partial vacuum. The crude product thereby obtained is chromatographed on a column of silica gel (HPLC) using the eluant ethyl acetate/hexane (7:3), leading to the isolation of 4.4 g (65% yield) of pure 2'-O-(13-cis-retinoyl)erythromycin A.

M.p. 82°C (hexane/ethyl acetate)

$[\alpha]_D^{22}$ = -17° (C = 6 mg/ml, dichloromethane)

Microanalysis : $C_{57}H_{93}NO_{14}$; M = 1016.4

	C	H	N
Calculated % :	67.36	9.22	1.38

Found % : 67.48 9.32 1.38

Infrared : band at 1735 cm^{-1} (ester)

^{13}C NMR ($CDCl_3$, internal ref. TMS)

Negative γ effects at the 1'-position (-2.2 ppm) and 3'-position (-2.1 ppm), indicate the 2'-position of the ester. Carbons $C"_{20}$ (20.94 ppm), $C"_{14}$ (117.28 ppm) and $C"_{12}$ (131.9 ppm) of the retinoic chain are in agreement with the 13-cis stereochemistry of the retinoic chain.

PREPARATION EXAMPLE 2

Preparation of 2'-O-(all-trans-retinoyl)erythromycin A

5 g (16.6 mmol) of all-trans-retinoic acid are dissolved in 35 ml of anhydrous tetrahydrofuran in a round-bottomed flask and under an inert atmosphere, the reaction mixture is cooled to 0°C and then 3 ml (38 mmol) of anhydrous pyridine and 1.6 ml (16.6 mmol) of ethyl chloroformate are poured in; the solution is stirred for 5 minutes and 2.5 g (30 mmol) of sodium hydrogen carbonate are added, followed by 4.9 g (6.7 mmol) of erythromycin A, previously dissolved in 150 ml of tetrahydrofuran. The reaction mixture is then left with stirring for 10 hours while being allowed to return to room temperature (thin layer chromatography on silica gel: methylene chloride/methanol, 10%). The solution is poured into 60 ml of water and then extracted with ethyl acetate. The organic phase is dried over magnesium sulphate, filtered and then concentrated under partial vacuum. The crude product

thereby obtained is chromatographed on a column of silica gel (HPLC) using the eluant ethyl acetate/hexane (7:3), leading to the isolation of 4.1 g (60% yield) of pure 2'-O-(all-trans-retinoyl)erythromycin A.

$[\alpha]_D^{22}$ = -65° (C = 2 mg/ml, dichloromethane)

Microanalysis : $C_{57}H_{93}NO_{14}.4H_2O$; M = 1088.5

	C	H	N
Calculated % :	62.89	9.35	1.29
Found % :	62.91	8.90	1.29

^{13}C NMR ($CDCl_3$, internal ref. TMS)

Negative γ effects at the 1'-position (-2 ppm) and 3'-position (-1.9 ppm), indicate the 2'-position of the ester. Carbons $C"_{20}$ (14.1 ppm), $C"_{14}$ (119.36 ppm) and $C"_{12}$ (135.19 ppm) are in agreement with the all-trans stereochemistry of the retinoic chain.

PREPARATION EXAMPLE 3

Preparation of 3-O-(all-trans-retinoyl)clindamycin

5 g (16.6 mmol) of all-trans-retinoic acid are dissolved in 30 ml of anhydrous tetrahydrofuran in a round-bottomed flask and under an inert atmosphere; the reaction mixture is cooled to 0°C and then 6 ml (76 mmol) of anhydrous pyridine and 1.6 ml (16.6 mmol) of ethyl chloroformate are poured in; the solution is stirred for 5 minutes and 1.25 g (15 mmol) of sodium hydrogen carbonate are added, followed by 2.35 g (5.5 mmol) of clindamycin, previously dissolved in 100 ml of a tetrahydrofuran/pyridine (8:2) mixture. The reaction mixture

is then left with stirring for 10 hours while being allowed to return to room temperature (thin layer chromatography on silica gel: methylene chloride/methanol 5%). The solution is poured into 80 ml of water and then extracted with ethyl acetate. The organic phase is dried over magnesium sulphate, filtered and then concentrated under partial vacuum. The crude product thereby obtained is chromatographed on a column of silica gel (HPLC) using the eluent ethyl acetate/hexane (5:5), leading to the isolation of 2.15 g (55% yield) of pure 3-O-(all-trans-retinoyl)clindamycin.

M.p. 62°C

$[\alpha]_D^{22}$ = +50° (C = 100 mg/ml, dichloromethane)

Microanalysis : $C_{38}H_{59}N_2SO_6Cl.2.5H_2O$; M = 752.5

	C	H	N
Calculated % :	60.44	8.08	3.23
Found % :	60.66	8.57	3.72

^{13}C NMR ($CDCl_3$, internal ref. TMS): negative effects at the 4-position (-2.8 ppm) and 2-position (-1.9 ppm). The chemical shifts of C"$_{14}$ (117.84 ppm) and C"$_{20}$ (14.11 ppm) confirm the all-trans stereochemistry of the retinoyl chain.

PREPARATION EXAMPLE 4

Preparation of 3-O-(13-cis-retinoyl)clindamycin

5 g (16.6 mmol) of 13-cis-retinoic acid are dissolved in 30 ml of anhydrous tetrahydrofuran in a round-bottomed flask and under an inert atmosphere; the reaction

mixture is cooled to 0°C and then 6 ml (76 mmol) of anhydrous pyridine and 1.6 ml (16.6 mmol) of ethyl chloroformate are poured in; the solution is stirred for 5 minutes and 1.25 g (15 mmol) of sodium hydrogen carbonate are added, followed by 2.35 g (5.5 mmol) of clindamycin, previously dissolved in 100 ml of a tetrahydrofuran/pyridine (8:2) mixture. The reaction mixture is then left with stirring for 10 hours while being allowed to return to room temperature (thin layer chromatography on silica gel; methylene chloride/methanol 5%). The solution is poured into 80 ml of water and then extracted with ethyl acetate. The organic phase is dried over magnesium sulphate, filtered and then concentrated under partial vacuum. The crude product thereby obtained is chromatographed on a column of silica gel (HPLC) using the eluant ethyl acetate/hexane (5:5), leading to the isolation of 2 g (51% yield) of pure 3-O-(13-cis-retinoyl)-clindamycin.

M.p. 95°C (hexane/ethyl acetate)

$[\alpha]_D^{20}$ = +111° (C = 15 mg/ml, dichloromethane)

Microanalysis : $C_{38}H_{59}ClN_2SO_6$; M = 707.4

	C	H
Calculated % :	64.52	8.41
Found % :	64.47	8.45

^{13}C NMR ($CDCl_3$, internal ref. TMS)

The position of the ester is indicated by the positive β effect at the 3-position (+1.77 ppm) and the

negative γ effects at the 2-position (-1.4 ppm) and 4-position (-2.5 ppm). The 13-cis configuration is confirmed by C''_{20} (20.93 ppm) and C''_{14} (115.94 ppm).

PREPARATION EXAMPLE 5

Preparation of 3-O-(13-cis-retinoyl)lincomycin

5 g (16.6 mmol) of 13-cis-retinoic acid are dissolved in 30 ml of anhydrous tetrahydrofuran in a round-bottomed flask under an inert atmosphere; the reaction mixture is cooled to 0°C and then 6 ml (76 mmol) of anhydrous pyridine and 1.6 ml (16.6 mmol) of ethyl chloroformate are poured in; the solution is stirred for 5 minutes and 1.25 g (15 mmol) of sodium hydrogen carbonate are added, followed by 2.2 g (5.4 mmol) of lincomycin, previously dissolved in 100 ml of a tetrahydrofuran/pyridin (7:3) mixture. The reaction mixture is then left with stirring for 10 hours while being allowed to return to room temperature (thin layer chromatography on silica gel: methylene chloride/methanol, 10%). The solution is poured into 100 ml of water and then extracted with ethyl acetate. The organic phase is dried over magnesium sulphate, filtered and then concentrated under partial vacuum. The crude product thereby obtained is chromatographed on a column of silica gel (HPLC) using the eluant ethyl acetate/hexane (8:2), leading to the isolation of 1.85 g (50% yield) of pure 3-O-(13-cis-retinoyl)lincomycin.

M.p. 95° (hexane/ethyl acetate)

$[\alpha]_D^{20}$ = +103° (C = 7 mg/ml, dichloromethane)

Microanalysis : $C_{38}H_{60}N_2SO_7.2.5H_2O$; M = 734.5

	C	H
Calculated % :	62.18	9.03
Found % :	62.33	8.64

^{13}C NMR ($CDCl_3$, internal ref. TMS)

The position of the ester is indicated by the positive β effect at the 3-position (+1.6 ppm) and the negative γ effects at the 2-position (-2.4 ppm) and 4-position (-1.9 ppm). The 13-cis configuration is confirmed by C"20 (20.98 ppm) and C"14 (115.83 ppm).

PREPARATION EXAMPLE 6

Preparation of a mixture of 7-O-(all-trans-retinoyl)lincomycin, 3-O-(all-trans-retinoyl)lincomycin and 2-O-(all-trans-retinoyl)lincomycin monoesters

30 g (74 mmol) of lincomycin are dissolved in 300 ml of anhydrous N,N-dimethylformamide in a round-bottomed flask and under an inert atmosphere, 830 mg (7.4 mmol) of potassium tert-butylate are then added and stirring is continued at room temperature for 90 minutes. A solution of 13 g (37 mmol) of 1-(all-trans-retinoyl)imidazole in 150 ml of N,N-dimethylformamide is then poured in and the resulting mixture is stirred at room temperature for 12 hours (thin layer chromatography on silica gel: methylene chloride/methanol, 7.5%). The solution is poured into 500 ml of water and then extracted with ethyl acetate. The organic phase is dried over magnesium sulphate, filtered and then concentrated under partial vacuum.

The crude product thereby obtained is chromatographed on a column of silica gel (HPLC) using the eluant ethyl acetate/hexane (7:3), leading to the isolation of 39 g (77%) of a mixture of all-trans-retinoic monoesters of lincomycin at the 2-, 3- and 7-positions.

^{13}C NMR ($CDCl_3$, internal ref. TMS)

- Negative γ effects at the 8-position (-2.5 ppm) and the 6-position (-3.8 ppm) indicate the site of esterification of a monoester at the 7-position,
- Negative γ effect at the 1-position (-4 ppm) indicates the monoester at the 2-position, and negative γ effects at the 2-position (-2 ppm) and 4-position (-2.6 ppm) indicate the position of the monoester at the 3-position.

The positions of C_1 are at 85.06 ppm for the 2-monoester, at 88.45 ppm for the 7-monoester and at 89.67 ppm for the monoester at the 3-position.

The all-trans configuration of the retinoic chain is indicated for C"14 at 117.78 ppm and for C"20 at 14.08 ppm; a trace of isomerization is noted by the presence of a peak at 115.2 ppm (C"14) indicating the 13-cis isomer.

PREPARATION EXAMPLE 7

Preparation of a mixture of 2-O-(all-trans-retinoyl)clindamycin, 3-O-(all-trans-retinoyl)clindamycin and 4-O-(all-trans-retinoyl)clindamycin monoesters

20 g (47 mmol) of clindamycin are dissolved in 250 ml of an anhydrous N,N-dimethylformamide in a round-

bottomed flask and under an inert atmosphere, and 527 mg (4.7 mmol) of potassium tert-butylate are then added to the reaction medium, which is then stirred at room temperature for 90 minutes. A solution of 8.250 g (23.5 mmol) of 1-(all-trans-retinoyl)imidazole in 150 ml of anhydrous N,N-dimethylformamide is then poured in and the resulting medium is stirred at room temperature for 12 hours (thin layer chromatography on silica gel: methylene chloride/methanol, 5%). The solution is then poured into 500 ml of water, after which it is extracted with ethyl acetate. The organic phase is dried over magnesium sulphate, filtered and then concentrated under partial vacuum. The crude product thereby obtained is chromatographed on a column of silica gel (HPLC) using the eluant ethyl acetate/hexane (5:5), leading to the isolation of 28 g (85%) of a mixture of all-trans-retinoic monoesters of clindamycin at the 2-, 3- and 4-positions.

^{13}C NMR ($CDCl_3$, internal ref. TMS)

- Negative γ effect at the 1-position (-3 ppm) indicates the 2-position of the ester,
- Negative γ effects at the 4-position (-2.8 ppm) and 2-position (-1.9 ppm) indicate the monoester at the 3-position, and weak negative γ effect at the 3-position indicates the monoester at the 4-position.

The positions of C_1 are at 84.63 ppm for the 2-monoester, at 88.79 ppm for the 3-monoester and at 87.98 ppm for the 4-monoester.

The all-trans configuration of the retinoic chain is predominant (C"$_{14}$ at 117.5 ppm and C"$_{20}$ at 14.08 ppm), but there are clear traces of isomerization, in particular at C"$_{20}$ and C"$_{14}$.

EXAMPLE 1

ANTI-ACNE LOTION

The following composition is prepared:

Erythromycin		2	g
Octopirox		1	g
Butylated hydroxytoluene (BHT)/butylated hydroxyanisole (BHA) antioxidant		0.4	g
Water/isopropanol solution (60:40 by volume)	qs	100	g

EXAMPLE 2

ANTI-ACNE LOTION

The following composition is prepared:

Clindamycin		0.6	g
Octopirox		0.02	g
Benzoyl peroxide		2.5	g
Antioxidant (BHT, BHA)		0.1	g
Water/ethanol solution (60:40 by volume)	qs	100	g

EXAMPLE 3

ANTI-ACNE GEL

The following composition is prepared:

Erythromycin	2	g
Salicylic acid	0.5	g
Octopirox	2	g
Polyacrylic acid crosslinked with a polyfunctional agent, sold by the company B.F. GOODRICH under the trade name "CARBOPOL 941"	0.5	g
Antioxidant (BHT, BHA)	0.5	g
Ethanol	20	g
Water qs	100	g

EXAMPLE 4

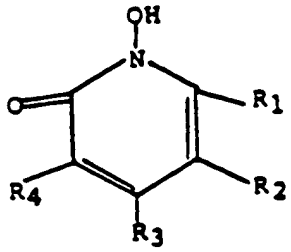
GEL

The following composition is prepared:

Erythromycin linoleate	3	g
Cyclopirox	1	g
Hydroxypropyl cellulose sold by the company HERCULES under the trade name "KLUCEL H"	1	g
Antioxidant (BHT, BHA)	0.1	g
Ethanol	20	g
Water qs	100	g

CLAIMS

1. A composition suitabl for topical application which comprises, in a physiologically acceptable medium, at least one pyridone derivative corresponding to the formula:



(I)

in which:

R_1 denotes hydrogen, linear or branched alkyl having from 1 to 17 carbon atoms, cycloalkyl having from 5 to 8 carbon atoms, cycloalkylalkylene, in which the alkylene group has from 1 to 4 carbon atoms, aryl, aralkyl in which the alkyl group has from 1 to 4 carbon atoms, arylalkenyl in which the alkenyl group has from 2 to 4 carbon atoms, such that the aryl and cycloalkyl groups can be substituted by an alkyl or alkoxy group having from 1 to 4 carbon atoms;

R_2 denotes hydrogen, alkyl having from 1 to 4 carbon atoms, alkenyl having from 2 to 4 carbon atoms, halogen or benzyl;

R_3 denotes hydrogen, alkyl having from 1 to 4 carbon atoms or phenyl; and

R_4 denotes hydrogen, alkyl having from 1 to 4 carbon atoms, alkenyl having from 2 to 4 carbon atoms, methoxy-methyl halogen, or a benzyl radical; or a cosmetically or pharmaceutically acceptable salt thereof, and at least one

antibacterial agent which is a macrolide antibiotic or pyranoside, or a salt or ester thereof.

2. A composition according to claim 1, in which R_1 denotes a cyclohexyl or linear or branched alkyl group and R_3 denotes a lower alkyl group, for example of 1 to 6 carbon atoms.

3. A composition according to claim 1 or 2, in which the compound of formula (I) is 6-cyclohexyl-1-hydroxy-4-methyl-2(1H)-pyridone or 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1H)-pyridone.

4. A composition according to any one of claims 1 to 3, in which the antibacterial agent is an erythromycin, clindamycin or lincomycin derivative.

5. A composition according to claim 4, in which the erythromycin derivative is erythromycin or an estolate, ethylcarbonate, ethylsuccinate, glucoheptonate, lactobionate, propionate lauryl sulphate, propionate, stearate, linoleate or monoenic, di- or trienic ester of erythromycin.

6. A composition according to claim 4, in which the clindamycin derivative is a hydrochloride, palmitate or phosphate, and the lincomycin derivative is lincomycin hydrochloride.

7. A composition according to any one of claims 1 to 6, in which the antibacterial agent is an erythromycin retinoate, clindamycin retinoate or lincomycin retinoate.

8. A composition according to any one of claims 1 to 7 which also contains a keratolytic agent.

9. A composition according to claim 8, in which the keratolytic agent is benzoyl peroxide, salicylic acid or resorcinol.

10. A composition according to any one of claims 1 to 9 which also contains S-carboxymethyl-cysteine, thiamorpholinone, S-benzylcysteamine or a derivative thereof or tioxolone.

11. A composition according to any one of claims 1 to 10 which also contains at least one steroidal or non-steroidal anti-inflammatory agent.

12. A composition according to claim 11, in which the anti-inflammatory agent is hydrocortisone, indomethacin, glycyrrhetinic acid, α-bisabolol, betamethasone, fluocinolone acetonide or desoxymethasone.

13. A composition according to any one of claims 1 to 12, in which the compound of formula (I) is present in an amount from 0.01 to 5% by weight, and in that the antibacterial agent is present in an amount from 0.01 to 5% by weight, relative to the total weight of the composition.

14. A composition according to any one of claims 1 to 13 which is in the form of a gel, pad, cream, lotion, spray, ointment or stick.

15. A composition according to any one of claims 1 to 14 which contains water or a mixture of water and a

lower alcohol, glycol or glycol ether.

16. A composition according to any one of claims 1 to 15 which also contains one or more thickening agents, antioxidants, colouring agents or perfumes.

17. A composition according to any one of claims 1 to 16, formulated for use in the therapeutic treatment of acne.

18. A composition according to any one of claims 1 to 16, formulated for use in the cosmetic treatment of the skin.

19. A composition according to claim 1 substantially as described in any one of Examples 1 to 4.

20. Use of the composition as defined in any one of claims 1 to 19, for the preparation of a medicinal product intended for treating acne.

21. Process for cosmetic treatment which comprises applying to the area to be treated a composition as defined in any one of claims 1 to 19.

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